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RESEARCH STUDENT	Miss.Shaikh Atiya Layakh Ali
MAIL ID.	Shaikhatiya31@gmail.com
MOBILE NO.	7385512709
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	Dr. Chaus Wajid Ahmed Nisar Ahmed
MAIL ID.	wajidchaus.dcop@gmail.com
MOBILE NO.	9970675785 / 7507700786
DESIGNATION	Assistant Professor and Head, Department of Pharmaceutics, Dayanand College of Pharmacy Latur
RESEARCH CENTRE	SCHOOL OF PHARMACY SRTMU NANDED
UNIVERSITY	SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY, NANDED-431606, (MAHARASHTRA STATE), INDIA.
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"FORMULATION, DEVELOPMENT AND EVALUATION OF NIOSOMAL GEL CONTAINING ANTIARTHRITIC DRUGS"

A SYNOPSIS SUBMITTED FOR THE REGISTRATION OF *DEGREE OF DOCTOR OF PHILOSOPHY*

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By

Miss.Shaikh Atiya L.
M. Pharm.

Under the Guidance of

Dr. Chaus Wajid Ahmed Nisar Ahmed
M. Pharm., Ph.D.

Assistant Professor and Head,

Department of Pharmaceutics,

Dayanand College of P harmacy, Latur.

स्वामी रामानंद तीर्थ
मराठवाडा विद्यापीठ,नांदेड.

Swami Ramanand Teerth Marathwada University,

Nanded-431606, (Maharashtra State), India.

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1. Abstract of proposed work plan/ problem:

The aim of present study is to formulation development and evaluation of niosomal gel containing antiarthritic drug. Conventional dosage forms are available for treatment of rheumatism however the product has drawback of poor bioavailability hepatic first pass metabolism and rapid elimination. These problems can be reduced by the niosomal gel formulation. Niosomal formulations will prepare by using various surfactants in the presence of cholesterol and stearylamine (SA) in different ratios by ether injection technique. They will evaluate for Appearance, pH, particle size (TEM& SEM), Drug content, entrapment efficiency and *in vitro* drug release. The optimized formulation will be formulated as gels using polymers in different ratios and evaluating for gelling capacity, pH, viscosity, *in-vitro* drug release, drug content, Stability Study, *in-vivo* study, skin permeation & anti-inflammatory study. Niosomal gel is a viable alternative to conventional dosage form by virtue of its ability to enhance bioavailability and provide localized drug delivery and ability to sustain drug release. And improves the skin permeation of topical formulation and prolongs the retention time in the target area at a therapeutic level thereby decreasing the frequency of administration and increasing patient compliance.

Key words: Targeted vesicular drug delivery, niosomes, and structure of niosomes arthritic pains.

2. Introduction:

Arthritis is the swelling and aching of one or more joints. There are mainly two common types of arthritis are rheumatoid arthritis and osteoarthritis. Rheumatoid arthritis (RA) is a long-term inflammatory autoimmune disease that affects joints. Osteoarthritis usually comes with age and most often affects the fingers, knees, and hips.[1-2] Arthritis is clinically manifested by stiffness of the joints, gradual loss of joint function, and long-lasting pain, which together leads to loss of self-support and disturbance of life. Whereas there is no cure for arthritis, symptomatic management can progress the quality of life of patients. This includes pain control using non-steroidal anti-inflammatory drugs (NSAID) analgesics, steroids.[3-4]

Anti-arthritic drugs are obtainable in the market as oral suspension, tablets or capsules. This antarthritic drug is a very weak acid, with a PKa value of 9.68 and it is very lipophilic in nature. It shows variable absorption profiles and delayed onset of action ranging from 3 to 4 hours after oral administration.[5]

Some conventional anti rheumatic drugs suffers hepatic first pass metabolism and rapid elimination from plasma.[6]The long-term use induces cardio toxicity after oral administration.

To progress therapeutic outcome and reduce the rate of adverse actions subsequently use modified novel drug delivery systems have been developed. Poor therapeutic efficiency and hepatic first-pass metabolism at targeted region are the common problems of new drug molecules. Consequently research has been carried out on the vesicular novel drug delivery systems in nanotechnology from the previous few years. These nano-carrier systems have developed to overcome the complications that are related with hepatic first-pass metabolism in conventional oral dosage forms and the barrier properties of the lipid bilayer in stratum corneum via transdermal drug delivery and also for improving the bioavailability of various drugs.

In current years, several targeted vesicular drug delivery carriers are developing like liposomes, niosomes, proniosomes, transferosomes, ethosomes, and electrosomes. Among them, niosomes are to be better carriers to increase therapeutic efficiency and bioavailability by reducing the side effects and acting as a promising approach for transdermal drug delivery.

Niosomes[7-11] is a targeted drug delivery system in which medication encapsulated in a vesicle. Vesicle composed of a bilayer of non-ionic surface active agent hence name as niosomes. Niosomes are microscopic small in size. Their size lies in nanometric scale. Niosomes have recently been shown to greatly increased transdermal drug delivery and also used in targeted drug delivery. It is mostly formed by cholesterol surfactants incorporation as an excipient. Other excipients are also used. Niosomes are unilamellar or Multilamellar vesicles. They are very similar to the liposomes.

Definition: Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant like span, tween, alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. In niosomes the vesicles forming amphiphiles is a non-ionic surfactant such as dicetyl phosphate, Stearyl amine. Both hydrophilic and lipophilic drugs are incorporated. Drug delivery by niosomes is potentially applicable to many pharmacological agents for their action against various diseases. Niosomes have shown potential in the release studies and serve as a better option for drug delivery system.

Components of niosomes: [12]

There are mainly three types of components are used for the preparation of niosomes:

1. Cholesterol, 2.Non-ionic surfactants, 3.Charged molecules

1. **Cholesterol:** Most important components of noisome is cholesterol. It forms hydrogen bond with the hydrophilic head of surfactant in the bilayer structure. It can influences some significant vesicular properties like entrapment efficiency, increase stability. It also promotes the stability of bilayer surface by influencing the gel liquid transition temperature. In case of surfactants having HLB >6is essential to form bilayer vesicles and for lower HLB value stability is improved by adding cholesterol. Its content also adjusts the loading capacity which is important factor for niosomal formulation. It has also been showed that incase of more hydrophobic surfactants addition of cholesterol helps in inhibiting the chance of aggregation and helps in vesicles formation.[13]
2. **Non-ionic surfactants:** Surfactants play a main role in the formation of niosomes. The following non-ionic surfactants are generally used for the preparation of niosomes the spans(span60,40,20,85,80),tweens (tween20,40,60,80) and Birijs (brij 30,35,52,58,72,76). The non-ionic surfactants have a hydrophilic head and a hydrophobic tail. The choice of

non-ionic surfactant depends upon Hydrophilic and Lipophilic balance (HLB), critical micellar concentration (CMC) and critical packing of parameter of amphiphiles

3. **Charged molecule:** Are mainly added to increase stability by providing charged groups to the bilayer surface. Dicetyl phosphate is mostly used as charged molecules which impart negative charged molecules on the bilayer surface are mainly added to increase stability of the vesicles and to prevent aggregation by providing charged groups to the bilayer surface. Dicetyl phosphate is mostly used charged molecules which impart a negative charge on the bilayer surface. Usually added in an amount of 2.5-5 mol%. Even so increasing the amount of charged molecules can suppress niosome preparation. Examples: Dicetyl phosphate (DCP)-inducing negative charge, Stearyl amine (SA) inducing positive charge.

Structure of Niosomes:[14-16] Niosome vesicles would consists of a vesicle forming amphiphilic i.e. Surfactant such as span 20,40,60,80 which is stabilized by the addition of cholesterol and a small amount of anionic surfactant such as Dicetyl phosphate which also helps in stabilizing the vesicles. These are microscopic lamellar structures which are formed on the admixture of non-ionic surfactant of alkyl or dialkyl polyglycerol ether class and cholesterol with hydration in aqueous media.

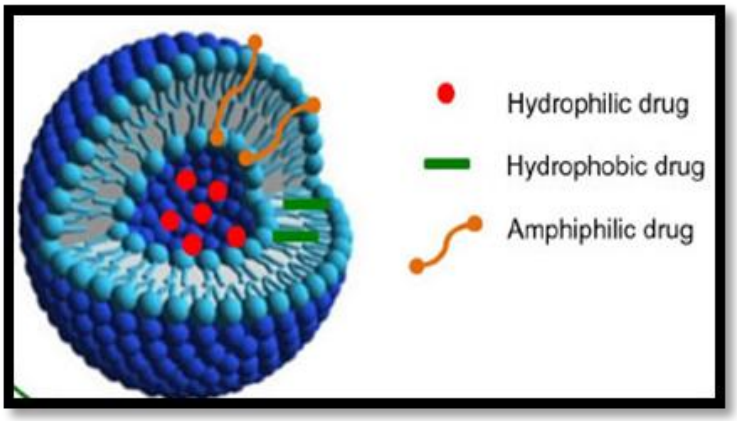

Figure No.1: Structure of Noisome

3. Review of Literature and Development in the subject (Previous work done in the relevant area):

Tejas Barot *et al.*, (2021) was developed and characterized *in vitro–in vivo* evaluation of Farnesol loaded niosomal gel for applications in oral candidiasis treatment. The aim of the study was to formulate and characterize the farnesol loaded niosomes comprising gel formulation and perform their *in vitro–in vivo* evaluation for applications in the treatment of oral candidiasis infections. By using different gelling systems were evaluated for their rheological and stability properties. Transmission electron microscopy (TEM) and Atomic force microscopy (AFM) were used to observe the niosomal surface morphology. Centrifugation method and dialysis method were used to find out the % entrapment efficiency (%EE) and *in-vitro* release of Farnesol, respectively. In-vitro antifungal effect and cell biocompatibility of the Farnesol loaded niosomal gel was also performed using Candida albicans (C. albicans) as the model organism and epithelial cell line (SW480) by MTT cytotoxicity assay. In-vivo skin irritation test was performed on rabbit skin. This novel niosome loaded gel-based formulation could make the oral candidiasis healing process more efficient while improving patient compliance. With the optimized methodology used in this work, such formulation approaches can become efficient, industrially scalable, and cost-effective alternatives to the existing conventional formulations.

Eman Alaaeldin *et al.*, (2021) was formulated topical nano-vesicular spanlastics of celecoxib enhanced anti-inflammatory effect and down regulation of TNF-α, NF-κB and COX-2 in complete freund's adjuvant-induced arthritis model in rat. The aim of this work was to achieve site-specific delivery of celecoxib-loaded spanlastic nano-vesicle-based delivery system to the inflamed joints, avoiding systemic administration of large doses. Methodology: To develop spanlastic nanovesicles for transdermal delivery of celecoxib, modified injection method was adopted using Tween 80 or Brij as edge activators. Entrapment efficiency, vesicle size, ex vivo permeation, and morphology of the prepared nano-vesicles were characterized. Carbopol-based gels containing the selected formulations were prepared, and their clarity, pH, rheological performance, and ex vivo permeation were characterized. Celecoxib-loaded niosomes and noisome-containing gels were developed for comparison. The in vivo efficacy of the selected formulations was

evaluated in a rat model of Freund's complete adjuvant-induced arthritis. Different inflammatory markers including TNF-α, NF-κB and COX-2 were assessed in paw tissue before and after treatment.

Bwalya A Witika *et al.*, (2021) was studied Vesicular drug delivery for the treatment of topical disorder current and future perspectives. Vesicular drug delivery has become a useful approach for therapeutic administration of pharmaceutical compounds. Several drug molecules are available for topical disorders. However, physicochemical properties and undesirable toxicity have limited their efficacy. Vesicular delivery systems have the potential to overcome these shortcomings due to properties such as high biocompatibility, simplicity of surface modification and suitability as controlled delivery vehicles. However, incorporating these systems into environmentally responsive dispersants such as hydrogels, ionic liquids and deep eutectic solvents may further enhance therapeutic prowess of these delivery systems. Consequently, improved vesicular drug delivery can be achieved by considering combining some of these formulation approaches.

Christian A. Alaloi *et al.*, (2020) was Evaluated diclofenac niosomal gel formulation with Grewia gum for topical delivery. The purpose of this study was to formulate niosomal gel for topical delivery of diclofenac using Grewia gum as gelling agent. Niosomes containing 1g of diclofenac were formed using the thin film hydration (TFH) method. Niosomal gels were then formulated using a semi-synthetic polymer, hydroxyl propyl methylcellulose (HPMC) and a natural polymer, Grewia gum as gelling agents. The formulated gels were evaluated for spreadability, viscosity, extrudability, homogeneity, clarity and pH. In this formulation Grewia gum at a concentration of 2% w/w could be used in the formulation niosomal gel for the delivery of diclofenac, which would help to circumvent the potential gastric irritation of diclofenac when used orally.

Snigdha Bhardwaj *et al.*, (2020) was developed and characterized niosomal gel system using lallementia royaleana benth mucilage for the treatment of rheumatoid arthritis. In present work, the attempt was made to identify the effect of different ingredients such as effect of Tweens and natural mucilage of Lallemantia royaleana Benth. on the performance of developed niosomal gel formulations in order to prolong the duration of action of drug and to minimize its side effects of topical conventional drug administration. All Ibuprofen loaded niosomes formulations will prepared by ether injection method;

using cetosteryl alcohol with different variants of Tweens and Spans. Various evaluation parameters were performed to confirm niosome formation. Further, the niosomes were incorporated into gel system and evaluated for in-vitro permeability study (ex-vivo) on excised rat skin by membrane diffusion method and invivo study by carrageenan induced rat paw edema model. The present study suggested that developed topical gel formulation provides enhance permeability and longer duration of drug action over conventional gels.

Sharma Rupali *et al.*, (2018) was developed and evaluated niosomal gel for transdermal application of steroidal API. The objective of this study was to develop a niosomalgel-based formulation system for testosterone steroidal molecule dissolved in a mixture of non-ionic surfactant and cholesterol in nanoparticulate form and evaluation of niosomal gel by different optimization parameters. The niosomal gel dispersion was prepared by heating system technique. The drug loaded niosomes showed much less vesicle size [10 - 500 nm] and good PDI, which means that the drug loaded can easily permeate the skin. Niosomal based gel was formulated by using the xanthan gum as gelling agent by optimizing different concentration of different gelling agents to get the best consistency of final niosomal gel. Various measurement parameters such as product quality, pH, purity, homogeneity, spread ability, viscosity, In vitro drug release, particle size determination, zeta potential, FTIR studies and TEM analysis were done to optimize the best batch.Entrapment efficiency was very good with value of 92.17 ± 0.02 percent. Niosomal gel has been found to exhibit strong consistency, good homogeneity, spread ability, viscosity parameters.Studies of FTIR showed no excipient interaction with the API molecule.

Kumar Ashish *et al.*, (2018) was formulated and evaluated of itraconazole niosomal gel. The present study was to formulate and evaluate the Itraconazole niosomal gel using surfactant span 40 and span 60 for the preparation of niosomes. The main objective of the study was to enhance the antifungal activity of the formulation. Itraconazole is a broad spectrum Imidazole derivative useful in the treatment of superficial and systemic fungal infection. Various surfactants used were span 40 and span 60. Niosomes were prepared by using Rotary Vaccum evaporation method. The drug content of the Itraconazole niosomal gel was determined at 262 nm against blank by using UV/visible spectrophotometer. The percentage of drug entrapment in niosomal gel was calculated to be 45.20% .The in-vitro

drug release study was carried out using phosphate buffer saline pH 7.4 and was found to be 41.18 ± 1.53% for 12 hours. It can be concluded that the gel formulation containing niosomes loaded with Itraconazole showed prolonged action than formulation containing Itraconazole in non-niosomal form and it can be developed successfully to improve the anti-fungal activity.

Irene Thomas *et al.*, (2018) was formulated and evaluated of niosomal gel of combined anti-fungal agents. miconazole, glucocorticoid antagonist and terbinafine, sqalene epoxidase inhibitor are two of the commonly used drug for fungal diseases. In this present work, Miconazole and Terbinafine in combination was formulated as Niosomal gel and evaluated. Niosomes were prepared by thin film evaporation technique with varying concentration of Nonionic surface active agent, Span 60 and cholesterol. Niosomal preparation evaluated for surface morphology, particle size, PDI, Drug content, entrapment efficiency, Zeta potential, in vitro drug release and TEM analysis. The formulation (N3) containing equal concentration of Span 60 (100 mg) and Cholesterol (100 mg) showed highest yield, drug content and its entrapment efficiency was found to be 91.06%. All the Niosomal dispersions were incorporated into 2% Carbopol gel base to produce Niosomal gels were evaluated for physical properties, pH, Viscosity, Spreadability, Extrudability, Drug content and in vitro drug release. Moreover Niosomal gel improves the topical formulation with a high degree of skin permeation and prolongs maintenance of drug by increasing the retention time in the target area.

Shaikh Karimunnisa* et al., *(2017) was developed and Evaluated of a Novel Drug Delivery System for Albendazole The main objective of the present study was to develop and evaluate long circulating pegylated niosomal formulation of albendazole (ABZ). It was imagined that pegylated niosomes would increase the systemic residence time of albendazole in the treatment of echinococcosis thus removing frequent doses of albendazole. Formulated by using span 60 pegylated with Distearoyl-sn-glycero-3-phosphoethanolamine (DSPE-PEG procured from Sigma Aldrich) were prepared by ethanol injection method. The prepared niosomes are evaluated for particle size, entrapment efficiency, zeta potential, in-vitro release and pharmacokinetic study. Niosomes of T90 pegylated was found to be twice (1440.8 min) as that of free dug (720.2 min). Thus pegylated niosomes prolonged the release of albendazole. Therefore by using

niosomal formulation reduce the frequency of administration of albendazole.

Gyati Shilakari Asthana et al., (2016) was investigated the delivery potential of Etodolac (ETD) containing topical niosomal gel. Niosomal formulations were prepared by thin film hydration method at various ratios of cholesterol and Span 60 and were evaluated with respect to particle size, shape, entrapment efficiency, and in vitro characteristics. Dicetyl phosphate (DCP) was also added in the niosomal formulation. Mean particle size of niosomal formulation was found to be in the range of 2 μm to 4 μm. Niosomal formulation N2 (1:1) ratio of cholesterol and surfactant displayed good entrapment efficiency (96.72%). TEM analyses showed that niosomal formulation was spherical in shape. Niosomal formulation (N2) displayed high percentage of drug release after 24 h (94.91) at (1:1) ratio of cholesterol: surfactant. Further selected niosomal formulation was used to formulate topical gel and was characterized with respect to its various parameters such as pH, viscosity, spreadability, ex vivo study, and in vivo potential permeation. Ex vivo study showed that niosomal gel possessed better skin permeation study than the plain topical gel. Further in vivo study revealed good inhibition of inflammation in case of topical niosomal gel than plain gel and niosomal formulation. The present study suggested that topical niosomal gel formulations provide sustained and prolonged delivery of drug.

Mohamed A. El-Nabarawi *et al* (2015) formulation and evaluation of topical niosomal gel of baclofen. The aim of the present study was to formulate topical gel containing baclofen niosomes. Baclofen is a direct agonist at GAPAB receptors with an anti-inflammatory effect. Baclofen has narrow therapeutic index and many gastrointestinal side effects. The current market products of baclofen are intrathecal injection and oral tablets which cause many problems after their administration, Thus, niosomal formulations as carriers for the topical delivery of baclofen will prolong the contact time and increase the permeability through the skin so improve its, as anti-inflammatory. The baclofen niosomes were prepared by altering the ratios between various non-ionic surfactants (Span 60, 40), cholesterol and charge inducing agents using thin film hydration method, the prepared niosomal formulations were evaluated for their encapsulation efficiency and maximum entrapment efficiency attained a maximum value of 80.31%, and characterized by transmission electron microscopy, differential scanning calorimetry, particle size analysis, zeta potential analysis and in vitro release after 24 hours. The maximum cumulative release

percentage was between 65.55%. Two gelling agents were used for the preparation of various baclofen gels and baclofen niosomal gels, in vitro permeation studies. Our results suggested that the niosomal delivery of baclofen in carbopol gel base acts as a suitable topical drug delivery system.

Alok Kumar Srivastav *et al.*, (2014) was studied the formulation of niosome of ofloxacin and its evaluation for efficacy of anti-microbial activity nanotechnology ,designing of Nano-carriers that can cross biological barriers and are able to target cellular reservoirs. The purpose of the present study was to formulate and evaluate niosomes. The niosomes were prepared by lipid film hydration method by using non-ionic surfactant i.e. span 60. Prepared formulation evaluated for morphological characterization, encapsulation efficiency, in-vitro drug release study. vesicle size and entrapment efficiency was found to be 100-300 nm, &78.4%.

Catalina danielastan *et al.*, (2013) was prepared and characterized niosomes containing metronidazole. The aim of present study the preparation and the characterization of non-ionic surfactant vesicles (NSV, niosomes) containing metronidazole are described. It is prepared by lipid film hydration technique using non-ionic surfactants with cholesterol at 1:2 and 1:1 ratio. Niosomes were characterized by melting points, by IR spectroscopy, by TG/DTG (thermogravimetry/derived thermogravimetry) and entrapment efficiency of metronidazole (metronidazole percent concentration). The highest entrapment efficiency was observed in the case of non-ionic surfactant/cholesterol use at 1:1 ratio.

Sanjeevani Desai *et al.*, (2011) was developed and evaluated of antifungal topical niosomal gel formulation Niosome are now widely studied as an alternative delivery system to liposome. In our present study we incorporated Nystatin into niosome by using ether injection method by applying 3^2 factorial designs. Prepared niosomes evaluated for size distribution, drug entrapment efficiency, zeta potential and drug release profile. Residence time of niosomes topically enhanced by developing niosomal gel formulation using carbomers. Developed niosomal gel was evaluated for pH, Spreadability, viscosity, drug content, drug release profile and ex vivo deposition study. Size & shape analysis confirmed by using TEM and Optical microscopy and was found to be in the range of 182-219 nm. The entrapment efficiency of the vesicles was determined by ultracentrifugation and was found to be in the range of 62-85%. The release from the niosomal gel was highly

prolonged when compared to conventional gel and showed two fold increases in the drug deposition in the skin compared to conventional gel.

Karandeep Kaur *et al.*, (2007) was formulated niosomal gel for site-specific sustained delivery of anti-arthritic drug *in vitro-in vivo* evaluation. Recently, cardio toxic effects associated with conventional modes of delivery of celecoxib have made it pertinent to develop alternate dosage forms capable of selectively delivering the drug topically to affected joints. The aim of the present study was to prepare and characterize niosomal gel formulation for sustained and site-specific delivery of celecoxib. Celecoxib loaded niosomes were prepared and characterized *in vitro, ex-vivo and in vivo*. The results of organ localization (deep skin layer + muscle) study showed that niosomal gel provided 6.5 times higher drug deposition as compared to carbopol gel (195.2±8.7 and 30.0±1.5, respectively). The muscle to plasma concentration ratio for niosomal gel formulation was six (2.16±0.12 μg/g vs. 0.34±0.01 μg/ml) and for carbopol gel it was one (0.36±0.01 μg/g vs. 0.43±0.02 μg/ml). Biological effectiveness of optimized formulation was evaluated using carrageen an induced rat paw edema model. The application of niosomal gel produced significant reduction of rat paw edema as compared to that after application of conventional gel indicating better skin permeation and deposition of celecoxib from niosomes. The results of the present study demonstrated niosomal gel formulation possess great potential for enhanced skin accumulation, prolonging drug release and improving the site specificity of celecoxib.

4. Aim & Objectives of Research/ Proposed Hypothesis:

Aim: Formulation development and evaluation of niosomal gel containing anti arthritic drugs.

Objectives of Research/ Proposed Hypothesis:

The objectives of present study are given below:

- To select anti arthritic drug with potent activity.
- To study compatibility of drug with excipient.
- To formulate niosomes using different ratios of non-ionic surfactant, cholesterol and drug by using ether injection technique.
- To carry out evaluation study as vesicle size and shape analysis by using SEM and TEM, Drug content, Percentage of entrapment efficiency, in-vitro drug release.
- To optimize the best formulation based on Entrapment efficiency and In-vitro drug release studies Drug content, and to develop niosomal gel.
- To carry out the evaluation studies i.e. Appearance, pH, Viscosity, FTIR, In-vitro study, Drug content, and *In-vivo* skin permeation study, anti-inflammatory Stability studies

5. Materials and Methodology to be adopted

Materials:

Drug: Anti arthritic drug

Surfactants: Span 20, 40, 60, 80 Tween 20,40,60,80 etc

Polymers: Carbapol-934p, 971p and 974p, Poloxamer, cholesterol etc.

Viscolisers: Hydroxy propyl methyl cellulose (HPMC), Methyl cellulose , (MC), Chitosan etc.

Preservative: Benzalkonium chloride, methyl paraben, propyl paraben.etc.

Other chemicals: Cholesterol, Triethanolamine, water, ethanol, methanol, diethyl ether, chloroform etc.

Instruments: Weighing balance, FTIR, pH-meter, Magnetic stirrer, SEM, TEM, UV Spectroscopy, Centrifuge, Brook field viscometer Sonicator Stability chamber, Refrigerator.

Method: Ether injection method: Niosomes prepared by using ether injection method in which Nonionic surfactant (NIS) (e.g. Span20, span40, span60, span80.) and cholesterol were taken in the different ratios (1:1, 1:2, 1:3 etc.) and dissolved in organic solvent (diethyl ether).The organic phase was slowly injected using 24-gauge needle into preheated 10 ml phosphate buffer containing drug which is magnetically stirred and maintained at temperature 40^0C -60^0C for 45 min. Stirring was continued until all ether evaporating to get drug loaded niosome. Vaporization of ether leads to formation of vesicles.

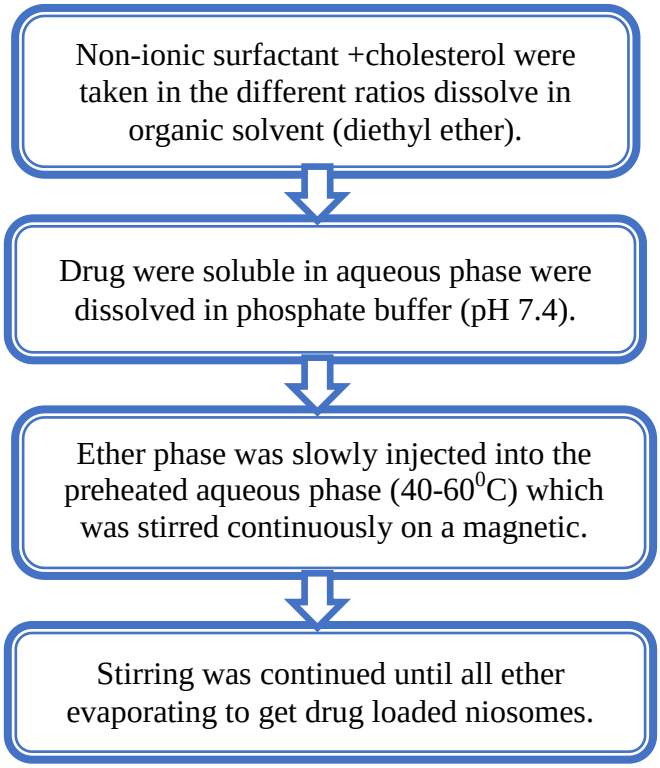
Non-ionic surfactant +cholesterol were taken in the different ratios dissolve in organic solvent (diethyl ether).
Drug were soluble in aqueous phase were dissolved in phosphate buffer (pH 7.4).
Ether phase was slowly injected into the preheated aqueous phase (40-60^{0}C) which was stirred continuously on a magnetic.
Stirring was continued until all ether evaporating to get drug loaded niosomes.

Figure No.2: Preparation of Niosomes

Preparation of Niosomal Carbopol gel:

Gelling agents (carbopol etc) at different concentration were added to water and kept in a dark for humectation up to 24 hrs. To obtain a gel ,gel pH was adjusted within the range of 6.8 – 7.2 by addition of triethanolamine. Select optimize batch of the niosomal dispersion was centrifuged and the pellet was separated and again dispersed in to the each concentration of the carbopol gel.

RESEARCH WORK PLAN

- **Literature Survey**
- **Collection of drug and Excipients**
- **Preformulation studies**

1) Organoleptic properties
2) Melting Point determination
3) Solubility profile of the drug
4) Calibration Curve
5) Compatibility studies by Fourier transform Infra-red Spectroscopy (FT-IR)

Formulations:

- **Preparation of Niosomes**
- **Evaluation of Niosomes**

1) Appearance
2) pH
3) Vesicles size & Shape analysis (SEM & TEM)
4) Drug content
5) % Entrapment Efficiency
6) Stability study
7) In-vitro drug release

- **Preparation of niosomal gel**
- **Evaluation of Niosomal gel**

1) Appearance
2) pH
3) Viscosity
4) Spreadability
5) Drug content
6) Stability study
7) In-vitro drug release
8) Skin Permeation and Deposition Study
9) Skin Toxicity Studies
10) Anti-inflammatory study

6. Importance of study/ Society application:

- The invention of Niosomes has becomes a significant step towards overcoming the problems associated with conventional dug delivery.
- Conventional dosage forms like celecoxib ,balofenac ibuprofen etc are used in treatment of rheumatism disease however the product has drawback of poor bioavailability hepatic first pass metabolism and rapid elimination,. These problems can be reduced by the niosomal gel formulation.
- Drug delivery through niosomes is one of the approaches to achieve localized drug action since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration.
- It results to enhancement of efficiency or potency of the same drug and at the same time reduces its systemic toxic effects.
- Thus niosomes entrapped through gel system has been developed to increase topical residence time, enhance topical bioavailability and reduce frequency of the administration of a drug.
- Niosomal gel for increasing biological half-life.
- To increase therapeutic efficiency.

7. International status / National status:

- International League of Associations for Rheumatology (WHO-ILAR) Community Oriented Program for Control of Rheumatic Diseases (COPCORD). They reported a prevalence of 0.51% (95% confidence interval [CI]: 0.3, 0.7) for RA diagnosed with ACR criteria and a prevalence of 0.6% (95% CI: 0.4, 0.9) for RA diagnosed clinically among nearly 6000 men and women 16 years or older (2998 men; 3000 women).
- Using the COPCORD surveys within urban and rural localities of Jammu, a prevalence of 0.7% was found by Mahajan *et al*. In a third COPCORD study, Joshi *et al*. surveyed over 8000 adults 16 years or older (4010 men and 4135 women) living in the Pune metropolis in Maharashtra. They recorded a crude prevalence of 0.28% (95% CI: 0.18, 0.42) for RA diagnosed with ACR criteria and a crude prevalence of 0.45 (95% CI: 0.32, 0.63) for RA diagnosed clinically. In a fourth study, Malaviya *et al*. surveyed five villages in the Ballabhgarh Township (Haryana) and reported a prevalence of 0.7% among nearly 40 000 men and women over 15 years of age.

- **Rheumatoid arthritis** - the Current Situation

  Among studies reporting a prevalence of RA or rheumatic symptoms for specific populations of patients, the prevalence ranged from 1.4% to 5.2%. In the Pune study previously referenced, there was a prevalence of 3.5% of RA among those with rheumatic musculo-skeletal diseases (RMSD). In the Jammu study previously referenced, a prevalence of 2.9% was found among the population with rheumatic disorders. In the eastern state of West Bengal, Kar *et al*. completed a cross-sectional study of clinical evaluations for 4800 new patients of all ages admitted to a hospital with rheumatological symptoms.

  A prevalence of 5.2% of RA among these patients was found. In the last prevalence study, the population of the Ottoor village of Kerala was surveyed after an epidemic of Chikungunya virus to assess rheumatic-musculoskeletal (RMSK) pain. In this village, the prevalence of RMSK pain was 1.4% among 437 individuals (mean age: 48 years).

- Only one study reported RA incidence among a population with rheumatic diseases. In this nationwide clinic study, 3000 doctors provided case records from over 11 900 clinic patients suffering from acute or chronic rheumatic conditions. The incidence among this patient population was 28%; however, the time period of data collection was not provided.
- The recommendations sign post to relevant clinical guidelines or outline evidence-informed care that will improve caring and optimise the use of healthcare resources. The recommendations provide a clinical navigation tool that aims to reduce the risk of rheumatism complications with swift escalation of treatment or service provision for those who develop such complications. These recommendations offer a framework for the development of local delivery plans that includes consideration of:
- Relevant research evidence (where it exists) to inform care.
- Configuration of services and deployment of workforce.
- Appropriate education for that workforce; and
- Relevant metrics to measure quality improvement.

►Significance of the study:

- About 1.5 million people in the world suffer from Rheumatoid Arthritis (RA). Nearly three times as many women have the disease as men. For treatment of RA many conventional dosage form are available
- The prepared topical niosomal gel would be highly beneficial to achieve better skin penetration, reducing the rheumatic inflammation as the required dose is decreased, and also circumvent the side effect of topical conventional drug administration**.**
- Niosomal gel has the potential for effective permeation enhancement at lower active concentrations than separate approaches. To overcoming the skin barrier in a safe and effective way either by chemical, physical or by vesicular nanotechnology based approaches, still remains a major challenge for topical applications.
- As there is progress in understanding the properties and the actual potential of these delivery systems, new pharmaceutical and cosmetic products based on these colloidal nano-gels can be considered as potential treatment formulations for management of rheumatoid arthritis.
- Newer and more versatile nano-gel such as nanoparticles, nano structured lipid carriers, cubosomes, exosomes self nano and micro-emulsifying drug delivery systems, etc are also explored in management of RA.
- In the near future, are likely to be developed for treatment of RA and other chronic ant inflammatory diseases. These formulations have potential to move to-wards clinics trails due to the ability to reduce drug dose, dosing frequency and side effects. Progression of RA along with new dosage regimen with nano formulations may significantly improve the quality of a RA patient.
- The development of a viable alternative to conventional topical gels as it provides sustained delivery. Moreover, the natural mucilage, used in the gel, possesses anti-inflammatory properties suggesting exerting a synergistic action of niosomal gel system at the target site to improve overall effect. Thus, it would be the better alternative that the niosomes loaded gel can be a promising potential drug delivery system for topical application to efficiently target local pains for prolonged periods and to reduce the frequency of application of gels as compared to conventional gels.

7. Proposed work Plan/ Formulation and Structure of Study:

Year-wise Plan of work and targets to be achieved:

Sr. No.	**Expected target to be achieved**	**1-6 months**	**7-10 months**	**11-22 months**	**22--27 months**	**28- 33 months**	**34-36 Month**
01	Literature survey	Literature survey					
02	Selection and collection of drug and excipients	Selection and collection of drug and excipients					
03	Formulation, development and optimization	Formulation, development and optimization					
04	Evaluation	Evaluation					
05	In vitro and in vivo study	In vitro and in vivo study					
06	Statistical Analysis, Data Interpretation and Conclusions	Statistical Analysis, Data Interpretation and Conclusions					
07	Publishing Research and submitting data	Publishing Research and submitting data					

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	Name of Research Candidate **Signature**	**Miss.Shaikh Atiya L.**
	Remarks of The Guide	
	Name and Designation of Research Supervisor **Signature**	Dr. Chaus Wajid Assistant Professor and Head, Department of Pharmaceutics, Dayanand College 0f Pharmacy, Latur.
	Remarks of Director/ Principal/ Head of The School/ Institution **Signature**	Dr. Director, (Seal of The School/Institute)